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Neutrophil/Lymphocyte ratio can distinguish transudate and exudate pericardial effusions

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Abstract
Aim: Early and definitive diagnosis is crucial in patients with pericardial effusion. Pericardial effusions can be caused by a variety of disorders and pericardiocentesis is required to identify whether the composition of the fluid is transudate or exudate. In this study, we compare the neutrophil/lymphocyte ratio (NLR) with the pericardial fluid protein/serum protein ratio to discriminate between transudates and exudates in pericardial fluid.
Material and Methods: Seventy-five of 107 consecutive patients who were admitted to a university tertiary-care center with new-onset large pericardial effusions who underwent pericardiocentesis between January 2013 and January 2018 were retrospectively analyzed. Clinical characteristics, final diagnosis, pericardial fluid and serum total protein measurements, and hematological parameters were retrieved from patients' charts. Patients were divided into two groups with regard to the nature of the pericardial fluid as exudate or transudate according to Light's criteria.
Results: The pericardial fluid protein/serum protein ratio and NLR were significantly higher in the exudate group than in the transudate group ($p<0.001$). Receiver operating characteristic curve analysis revealed that the NLR value of 3.93 was able to determine exudate pericardial fluid with 79.3% sensitivity and 82.4% specificity.
Discussion: The NLR might be used to identify the nature of pericardial fluid with high sensitivity and specificity before pericardiocentesis.

Keywords
Pericardial Effusion, Pericardiocentesis, Neutrophil, Lymphocyte, Transudates, Exudates

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Introduction

The pericardium surrounding the heart and great vessels consists of serous visceral and fibrous parietal layers. The pericardial cavity between these two layers contains 15-50 mL of serous fluid, which is essentially a plasma ultrafiltrate, consisting of myocardial interstitial fluid and lymphatic drainage [1]. Pathologies associated with the overproduction of pericardial fluid or obstruction in its drainage may lead to the development of pericardial effusion (PE) [2]. Most cases of PE result from the disruption of the permeability of inflamed pericardium or excessive fluid flow from the visceral pericardium.

Several classifications have been established to address the types of PE. One of the most common classifications involves categorizing the effusions as transudate, exudate, or both according to the composition of the effusion [3]. The distinction between exudate and transudate is helpful in revealing the etiology. Light's criteria are traditionally used to determine whether a pleural effusion is transudate or exudate in composition [4]. However, fluid aspiration, which exposes the patient to the risks of an invasive procedure, is required to utilize Light's criteria in the differential diagnosis of the fluid.

The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are readily available markers of systemic inflammation [5]. Previous studies have demonstrated that the NLR and PLR have diagnostic value in several pathologies characterized by the local or systemic inflammatory response, including coronary artery disease, diabetes mellitus, ulcerative colitis, tuberculosis, sarcoidosis, inflammatory arthritis, and Crimean-Congo hemorrhagic fever [6-9]. A recent study of 465 patients who underwent diagnostic thoracentesis for pleural fluid revealed that the NLR could facilitate the differential diagnosis of pleural effusion [10].

However, evidence regarding the role of the NLR in the differential diagnosis of the composition of PE is lacking. In this study, we aimed to investigate the role of the NLR in differentiating exudate and transudate PE.

Material and Methods

Seventy-five of 107 consecutive patients presenting to Adnan Menderes University's Faculty of Medicine with new-onset large pericardial effusions (>2 mm) who underwent pericardiocentesis between January 2013 and January 2018 were included in this cross-sectional descriptive study. Written informed consent for inclusion in the study was obtained from all patients. The study protocol was approved by the Institutional Ethics Committee (protocol no: 2018/1307, date: 18/01/2018).

All patients were imaged in the left lateral decubitus position using the same ultrasound system (VIVID 7, GE Vingmed Ultrasound, Horten, Norway) by two blinded observers. Two-dimensional and M-mode echocardiograms were obtained according to American Society of Echocardiography guidelines. PE was measured from the right ventricle, right atrium, posterior wall, and apex at end-diastole, when it is at its smallest at the fluid-tissue interface. A subxiphoid approach was used in all patients during the pericardiocentesis procedure. Patients' clinical features, the amount of pericardial fluid, serum levels of total protein, hematological parameters, and final diagnosis were recorded. Patients were divided into two groups according to the composition of the PE as exudate and transudate based on Light's criteria. The presence of one of the following criteria indicates exudate fluid: pleural fluid protein/serum protein ratio of >0.5, pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio of >0.6, or pleural fluid LDH >2/3 of the serum LDH upper limit of normal [4]. The NLR value was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The difference in NLR values between subjects with exudate and transudate PE was the primary outcome measure of this study. The predictive role of the NLR and PLR in identifying exudate PE was the secondary outcome measure.

Statistical Analysis

Normality of the continuous variables was evaluated with the Kolmogorov-Smirnov test. Parametric data are expressed as mean±SD and categorical data are expressed as percentages. Nonparametric variables are given as median values and ranges. The optimal cut-off point of the NLR at which the sensitivity and specificity would be maximal for the prediction of exudate was identified using receiver operating characteristic (ROC) curve analysis. Accuracy of the tests was measured using the area under the curve (AUC). Statistical analysis was performed with SPSS 14.0 (SPSS Inc., Chicago, IL, USA). Values of $p<0.05$ were considered statistically significant.

Results

The mean age of the study population was 61.80±15.90 years and 55% of the patients were male. Demographic characteristics of the study groups are given in Table 1. According to Light's criteria, 19 of the patients had transudate PE and 56 had exudate PE (Figure 1). The groups were similar with respect to age, diabetes, hypertension, alcohol consumption, smoking, echocardiographic findings, and the etiology of the PE. Laboratory measurements of the study population are presented in Table 2. There were no significant differences between the groups regarding laboratory measurements except

Table 1. Demographic features, final diagnosis, and echocardiographic measurements of the study groups

	Transudate PE n=19	Exudate PE n=56	p
Gender (male), n	12 (63%)	29 (52%)	0.390
Diabetes, n	4 (21%)	16(27%)	0.522
Hypertension, n	10 (53%)	23 (41%)	0.380
Alcohol, n	1 (5%)	0 (0%)	0.257
Smoking, n	4 (21%)	8 (14%)	0.487
Etiology			
Idiopathic, n	14 (74%)	38 (68%)	0.784
CRD , n	1 (5%)	4 (7%)	
Bacterial, n	0 (0%)	1 (2%)	
Malignity, n	2 (10%)	11 (20%)	
Tuberculosis, n	1 (5%)	1 (2%)	
Iatrogenic, n	1 (5%)	1 (2%)	
Ejection fraction, %	59.60±4.3	61.60±4.1	0.631
Size of the PE			
Right ventricle, mm	23.00±6.9	21.80±7.3	0.963
Right atrium, mm	18.60± 6.2	19.80±7.0	0.431
Posterior wall, mm	20.40±7.3	19.50±8.2	0.542
Apex, mm	19.90±7.3	19.00±8.5	0.214

Table 2. Laboratory findings of the study population

	Transudate PE n=19	Exudate PE n=56	p
Glucose, mg/dL	103.70±17.7	116.40±37.4	0.182
BUN, mg/dL	14.90 (11.90-41.20)	21.00 (14.50-36.20)	0.087
Creatine, mg/dL	0.80 (0.60-2.40)	0.90 (0.80-1.50)	0.965
AST, IU/L	26.00 (17.00-46.00)	22.00 (16.80-30.80)	0.476
ALT, IU/L	21.00 (14.00-31.00)	18.00 (11.00-31.80)	0.811
Cholesterol, mg/dL	156.00±45.0	157.30±51.4	0.950
HDL, mg/dL	39.10±9.2	40.60±16.4	0.805
LDL, mg/dL	94.90±45.0	99.70±37.4	0.759
Triglycerides, mg/dL	100 (73.50-151.00)	90.50 (72.50-115.00)	0.528
CRP, mg/L	121.90 (37.70-224.40)	96.30 (29.30-178.50)	0.240
Sedimentation rate, mm/h	49.50 (9.30-62.30)	75.00 (45.00-86.50)	0.117
Procalcitonin, ng/mL	0.60 (0.10-1.60)	0.20 (0.10-0.40)	0.266
Hemoglobin, g/dL	11.30±2.6	11.20±1.7	0.874
WBC, mm3	8.20 (6.40-12.40)	10.70 (7.70-13.80)	0.120
Neutrophils, mm3	4.80 (3.30-8.10)	8.50 (5.60-10.80)	0.004
Lymphocytes, mm3	1.90 (1.10-2.70)	1.30 (0.70-1.70)	0.002
MPV, fL	10.00±1.2	9.90±1.1	0.895
Platelets, mm3	312.00 (229.00-350.50)	272.00 (193.20-354.70)	0.294

ALT: Alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrgen, CRP: C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MPV: mean platelet volume, PE: pericardial effusion.

Table 3. Protein levels and the NLR values of the study groups

	Transudate PE n=19	Exudate PE n=56	p
Serum protein (g/dL)	6.70±0.9	6.20±0.8	0.060
Pericardial fluid protein (g/dL)	2.70±0.6	5.00±1.0	<0.001
PF protein/serum protein ratio	0.40±0.1	0.80±0.1	<0.001
NLR	2.90 (2.00-3.80)	6.00 (4.1-14.5)	<0.001

NLR: Neutrophil/lymphocyte ratio, PE: pericardial effusion, PF: pericardial fluid.

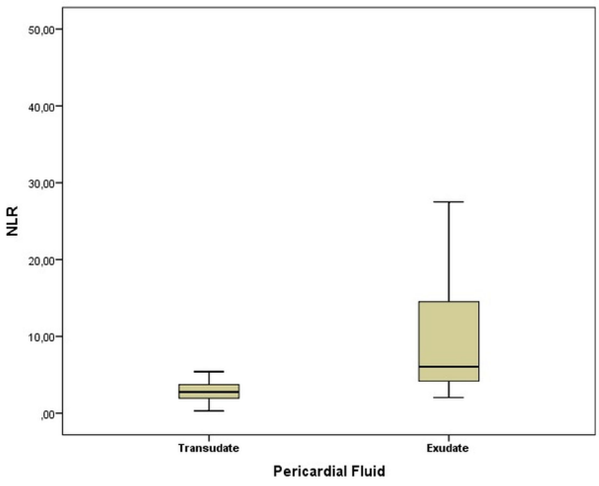

Figure 1. Flowchart demonstrating patient enrollment

for neutrophil and lymphocyte counts. The neutrophil count was significantly higher in the transudate PE group compared to the exudate PE group [4.80 (3.30-8.10)/mm3 vs. 8.50 (5.60-10.80)/mm3, p=0.004], whereas the lymphocyte count was significantly higher in the transudate PE group than the exudate PE group [1.90 (1.10-2.70)/mm3 vs. 1.30 (0.70-1.70)/mm3, p=0.002].

Total protein levels of serum and pleural fluid, the ratio of pleural fluid protein to serum protein, and NLR values of the transudate and exudate groups are shown in Table 3. Among these parameters, the total protein level of pleural fluid, the ratio of pleural fluid protein to serum protein, and NLR values were significantly higher in the exudate PE group than the transudate PE group (p<0.001 for all). There was a significant correlation between the NLR and the ratio of pleural fluid protein to serum protein (r=0.363, p=0.001).

ROC analysis revealed that a cut-off value of 3.93 for NLR was predictive for exudate PE with 79.3% sensitivity, 82.4% specificity, 93.9% positive predictive value, and 53.8% negative predictive value (AUC: 0.852, 95% confidence interval: 0.762-0.942, p<0.001) (Figure 2).

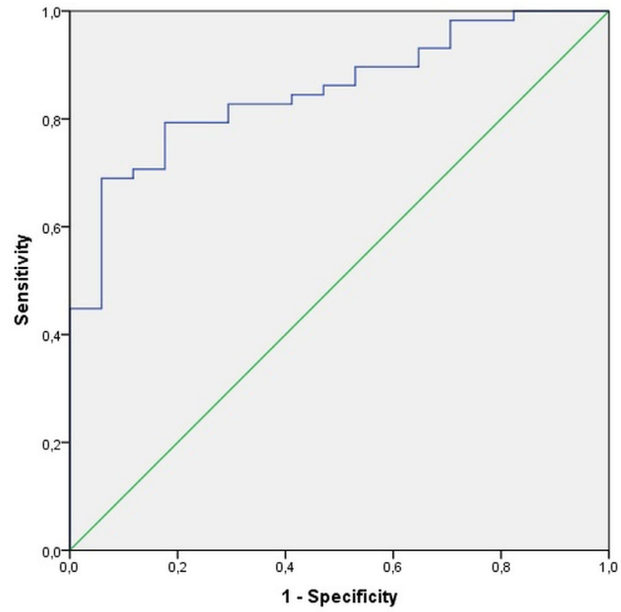

Figure 2. ROC analysis of NLR for identifying pericardial effusions with exudate composition

Discussion

This study is the first in the literature to demonstrate that the NLR might be utilized in identifying the composition of the fluid in patients with PE without fluid sampling. The results of this study indicate a strong relationship between the NLR and the pericardial fluid protein/serum protein ratio. Moreover, our findings show that NLR values of ≥3.93 may identify the exudate composition of the PE with high sensitivity and specificity.

Inflammation plays a crucial role in many cardiovascular disorders [11]. Growing evidence about the role of inflammation in various cardiovascular diseases has led to studies focusing on high-sensitivity C-reactive protein (hs-CRP) and other inflammatory markers for risk evaluation and the monitoring of disease activity [12, 13]. Total white blood cell count is an easily obtained marker of systemic inflammation. Previous studies have reported a positive correlation between acute phase reactants and proinflammatory proteins such as hs-CRP, tumor necrosis factor-α, interleukin-1 and interleukin-6, and leukocyte subtypes in nonspecific inflammatory conditions [14-16].

Recent trials have shown that increased platelet counts may indicate underlying inflammation as numerous inflammatory mediators stimulate megakaryocytic proliferation and produce

relative thrombocytosis. Furthermore, lymphocytopenia is a common finding during inflammation as a consequence of the increased levels of corticosteroid during the stress response [17]. In addition, lymphocytopenia may result from the increased lymphocyte apoptosis in critical inflammatory conditions [18, 19]. Therefore, the NLR represents both the inflammatory status and the stress response of the body.

Recently, the NLR has been found associated with negative outcomes in various cardiovascular diseases [20, 21]. As an inflammatory marker, NLR is associated with negative outcomes in acute coronary syndromes and recurrence of arrhythmias after cryoablation [22]. In addition, the NLR has also been associated with the presence of spontaneous echo contrast in patients with mitral stenosis and increased risk for stroke [23].

Although the NLR and PLR have been shown to be related to etiologies and outcomes in various clinical settings, their roles in idiopathic pleural effusion need to be clarified. In a previous study in our clinic, we found that the NLR and PLR were significantly higher in patients with PE compared to those without PE and we showed a positive correlation between the NLR and the amount of effusion in patients with idiopathic PE [24]. In a recent trial, Akturk et al. investigated the utility of the NLR in the differential diagnosis of pleural effusion [10]. Those authors found that the mean NLR was significantly higher in cases of malignant, para-pneumonic, and para-malignant pleural effusions compared to tuberculosis-related pleural effusions. They also stated that the role of the NLR in differential diagnosis among malignant, para-pneumonic, and para-malignant effusions was limited due to the close NLR values seen for these conditions.

The present study shows for the first time that the NLR might be utilized in the differentiation of transudate and exudate fluids in patients with PE in a noninvasive manner. Appropriate use of the NLR in cases of PE is likely to tailor the choice of further diagnostic tests. From this point of view, utilization of the NLR for these patients might prevent implementation of invasive diagnostic tests in cases of PE. A possible explanation for our results may be the high number of subjects with idiopathic PE, which has been shown to be associated with viral infections in previous studies [25]. Given that viral infections are associated with the collection of exudative fluid, the high number of patients with idiopathic PE, which is particularly likely to be viral in origin, might have led to the collection of exudative PE in our study population.

This study has some limitations that must be mentioned. The sample size was small and the proinflammatory markers measured in our study population were limited to complete blood count parameters, CRP, and erythrocyte sedimentation rate. Utilization of additional markers of inflammation such as cytokines might help to address the association between the NLR and other inflammatory markers more thoroughly.

Conclusion

Discriminating the composition of the fluid before the development of pericardial tamponade is the first step of early diagnosis and treatment of PE. We conclude that the NLR, a readily available and simple measure of inflammatory states, might be helpful in estimating the composition of PE before pericardiocentesis and may consequently prevent the development of the complications related to this procedure.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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